(a) Clarification as to the Patents on Which the Rejection is Based

U.S. Patent No. 5,346,708, which is entitled "Thermoplastic bag with separate handle and method of making same" is assigned to W.R. Grace & Co. It is not commonly owned or assigned with the subject application. Moreover, none of the inventors are the same and their subject matters are unrelated. Accordingly, a double patenting rejection based on U.S. Patent No. 5,346,708 is improper. Applicants assume that "5,346,708" is a typographical error, and that 5,246,708 was intended instead.

There is no U.S. Patent No. 8,060,459. To date all issued U.S. Patents have a number less than 8,000,000. Applicants assume that "8,060,459" is a typographical error, and that 6,060,459 was intended instead.

(b) 35 U.S.C. § 121 Prohibits Rejection Over Patent No. 5,736,531, No. 5,968,914 and No. 6,344,447

The subject application is a divisional of U.S. Application No. 08/176,485 (the '485 application), now U.S. Patent No. 5,736,531 (the '531 patent). U.S. Patent No. 5,968,914 (the '914 patent) issued from Application No. 08/472,210 (the '210 application), which is a continuation-in-part of the '485 application. U.S. Patent No. 6,344,447 (the '447 patent) issued from U.S. Application No. 09/249,790, which is a continuation of the '210 application. The claims of the '485 application were restricted (June 28, 1994) among three inventions, as follows: Group I (drawn to methods for preventing or treating the toxicity caused by pyrimidine nucleosides), Group II (drawn to methods for treating cancer) and Group III (drawn to compositions of acylated pyrimidine nucleosides and a chemotherapeutic agent). The subject matter of Group I

is being pursued in the present application. The subject matter of Group II is claimed in the '914 patent and the '447 patent, and the subject matter of Group III is claimed in the '531 patent. Therefore 35 U.S.C. § 121 prohibits using either the '914 patent, the '447 patent or the '531 patent as a reference against this application.

Moreover, the restriction requirement in the '485 application is evidence that methods for preventing or treating the toxicity caused pyrimidine nucleoside analogs are patentably distinct over: (1) methods for treating cancer; and (2) compositions. This evidence will be referred to below when considering the impropriety of the remaining obviousness-type double patenting rejections.

(c) Patentable Over U.S. Patent No. 6,329,350, No. 5,691,320 and 6,232,298

The rejection focuses primarily on U.S. Patent No. 6,329,350 (the '350 patent), and sweeps in the other reference patents by asserting that they are all "of same scope" and are "deemed same or substantial same" with each other and with the claims pending in the subject application.

The claims of the '350 patent are directed to methods for treating cancer. But, as seen from the restriction requirement in the '485 application (discussed above), methods for preventing or treating toxicity caused by pyrimidine nucleoside analogs are patentably distinct from methods for treating cancer. Accordingly, the claims of the subject application and the claims of the '350 patent are patentably distinct.

The claims of U.S. Patent No. 5,691,320 (the '320 patent) are directed to methods for treating or preventing tissue damage due to systemic inflammatory

response syndrome, for treating or preventing sepsis, and for reducing the toxicity of a therapeutic cytokine or inflammatory stimulus. The claims of U.S. Patent No. 6,232,298 (the '298 patent) are directed to methods for treating cachexia. They are not directed to methods for treating cancer. Thus the rejection is wrong to assert that they are of the same scope as the '350 patent or the pending claims.

The reasoning presented in the rejection is limited to the alleged lack of patentable distinction between methods for treating cancer as claimed in the '350 patent and methods for preventing or treating toxicity due to a pyrimidine nucleoside analog as claimed in the subject application. Because the claims of the '320 patent and the '298 patent are not directed to methods for treating cancer, no reasoning has been presented explaining why the claims of the subject application are supposed to be unpatentable over the claims of either the '320 patent or the '298 patent.

(d) Patentable Over U.S. Patent No. 5,583,117, No. 5,470,838, No. 6,258,795, No. 6,274,563 and No. 6,316,426

The claims of U.S. Patent No. 5,583,117 are directed to methods of delivering exogenous uridine or cytidine to the tissue of an animal, of treating cardiac insufficiency, and of treating myocardial infarction. The claims of U.S. Patent No. 5,470,838 are directed to methods delivering exogenous uridine or cytidine to the tissue of an animal, of treating cardiac insufficiency, of treating cirrhosis of the liver, and of treating myocardial infarction. The claims of U.S. Patent No. 6,258,795 are directed to certain acyl derivatives of uridine or cytidine, and pharmaceutical compositions containing such acyl derivatives. The claims of U.S. Patent No. 6,274,563 are directed to methods for

treating diabetes and diabetic neuropathy. The claims of U.S. Patent No. 6,316,426 are directed to methods for treating a central nervous system disorder. They are not directed to methods for treating cancer. Thus the rejection is wrong to assert that they are of the same scope as the '350 patent or the pending claims.

The reasoning presented in the rejection is limited to the alleged lack of patentable distinction between methods for treating cancer as claimed in the '350 patent and methods for preventing or treating toxicity due to a pyrimidine nucleoside analog as claimed in the subject application. Because the claims of the '117 patent, the '838 patent, the '795 patent, the '563 patent and the '426 patent are not directed to methods for treating cancer, no reasoning has been presented explaining why the claims of the subject application are supposed to be unpatentable over the claims of any of the '117 patent, the '838 patent, the '795 patent, the '563 patent and the '426 patent.

(e) Patentable Over U.S. Patent No. 6,403,565, No. 6,417,170 and No. 6,465,440

The claims of U.S. Patent No. 6,403,565 are directed to various methods relating generally to protecting or treating the skin of a mammal, such as reducing mutation frequency in the skin of mammals that have been exposed to ultraviolet radiation or other mutagens. The claims of U.S. Patent No. 6,417,170 are directed to a method for inducing regression of inflammatory or hyperproliferative skin lesions. Examples of skin lesions treated by the method of the '170 patent include melanoma, basal cell carcinoma and squamous cell carcinoma (Claim 2). The claims of U.S. Patent No. 6,465,440 are directed to a composition comprising a source of an individual nucleoside

with an agent that enhances skin penetration or a sunscreen agent. But, as seen from the restriction requirement in the '485 application, methods for preventing or treating the toxicity caused pyrimidine nucleoside analogs are patentably distinct over: (1) methods for treating cancer; and (2) compositions.

(f) Patentable Over U.S. Patent No. 6,472,378

The claims of U.S. Patent No. 6,472,378 are directed to pyruvyl derivatives of uridine. They are not directed to methods for treating cancer. Thus the rejection is wrong to assert that they are of the same scope as the '350 patent or the pending claims.

The reasoning presented in the rejection is limited to the alleged lack of patentable distinction between methods for treating cancer as claimed in the '350 patent and methods for preventing or treating toxicity due to a pyrimidine nucleoside analog as claimed in the subject application. Because the claims of the '378 patent are not directed to methods for treating cancer, no reasoning has been presented explaining why the claims of the subject application are supposed to be unpatentable over the claims of the '378 patent.

(g) Patentable Over U.S. Patent No. 6,020,322, No. 6,103,701, No. 6,297,222, No. 6,306,834, and No. 6,348,451

The claims of U.S. Patent No. 6,020,322 are directed to a method for cellular damage induced by radiation or other mutagens. The claims of U.S. Patent No. 6,297,222 are directed, *inter alia,* to certain acyl derivatives of 2'-deoxycytidine and a

pharmaceutical composition containing acyl derivatives of 2'-deoxycytidine and 2'-deoxyuridine. But, as seen from the restriction requirement in the '485 application, methods for preventing or treating the toxicity caused pyrimidine nucleoside analogs are patentably distinct over: (1) methods for treating cancer; and (2) compositions.

The claims of U.S. Patent No. 6,103,701 are directed to a method of enhancing hematopoiesis. The claims of U.S. Patent No. 6,306,834 are directed, *inter alia,* to methods of enhancing the delivery of exogenous 2'-deoxycytidine or 2'-deoxythymidine. The claims of U.S. Patent No. 6,348,451 are directed to a method for promoting wound healing. They are not directed to methods for treating cancer. Thus the rejection is wrong to assert that they are of the same scope as the '350 patent or the pending claims.

The reasoning presented in the rejection is limited to the alleged lack of patentable distinction between methods for treating cancer as claimed in the '350 patent and methods for preventing or treating toxicity due to a pyrimidine nucleoside analog as claimed in the subject application. Because the claims of the '701 patent and the '834 patent are not directed to methods for treating cancer, no reasoning has been presented explaining why the claims of the subject application are supposed to be unpatentable over the claims of the '701 patent or the '834 patent.

(h) Patentable Over U.S. Patent No. 6,054,441 and No. 6,060,459

The claims of U.S. Patent No.6,054,441 are directed to certain oxypurine nucleoside compounds. The claims of U.S. Patent No. 6,060,459 are directed to certain treatment methods utilizing oxypurine nucleoside compounds. Contrary to the rejection,

there is no overlap between the pending claims and the claims of the '441 patent or the '459 patent.

(i) Patentable Over U.S. Patent No. 6,020,320 and No. 6,743,782

The claims of U.S. Patent No. 6,020,320 are directed to methods of healing skin wounds, damaged liver tissue, or bone marrow. The claims of U.S. Patent No. 6,743,782 are directed to methods for enhancing the delivery of exogenous deoxyribonucleosides. They are not directed to methods for treating cancer. Thus the rejection is wrong to assert that they are of the same scope as the '350 patent or the pending claims.

The reasoning presented in the rejection is limited to the alleged lack of patentable distinction between methods for treating cancer as claimed in the '350 patent and methods for preventing or treating toxicity due to a pyrimidine nucleoside analog as claimed in the subject application. Because the claims of the '320 patent and the '782 patent are not directed to methods for treating cancer, no reasoning has been presented explaining why the claims of the subject application are supposed to be unpatentable over the claims of the '320 patent or the '782 patent.

(i) Patentable Over U.S. Patent No. 5,770,582 and No. 6,255,290

The claims of U.S. Patent No. 5,770,582 are directed to certain pharmaceutical compositions containing 2'-deoxycytidine and 2'-deoxyguanosine. The claims of U.S. Patent No. 6,255,290 are directed to a method for reducing the chance of developing skin cancer. But, as seen from the restriction requirement in the '485 application,

methods for preventing or treating the toxicity caused pyrimidine nucleoside analogs are patentably distinct over: (1) methods for treating cancer; and (2) compositions.

For all of the above reasons, the outstanding double patenting rejections should be withdrawn. Such action is respectfully requested.

II. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 1-25 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement, on the ground that the specification, while enabling effects of uridine and cytidine derivatives such as triacetyluridine (tau); octanoyl uridine; diacetyldeoxycytidine; and palmitoyldeoxycytidine (specification: Examples, pages 60-106), allegedly does not reasonably provide enablement for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside. The Action asserts that the selection of compounds of an acylated derivative of a non-methylated pyrimidine nucleoside is too broad based on the compounds disclosed in Examples, pages 60-106. The Action further asserts that, in the absence of data disclosing the effectiveness of an acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 for preventing or treating toxicity in an animal, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. This rejection is respectfully traversed.

At the outset, is noted that it is the USPTO, and not the Applicant, which bears the burden of establishing that an application does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated in In re Marzocchi:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367 (CCPA, 1971), (underlining added)

It is not sufficient for the USPTO to simply assert lack of enablement without also providing support for its position. As further stated in In re Marzocchi:

> "In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d at 224, 169 USPQ at _ (internal citations omitted) (underlining added)

In the outstanding Action, the USPTO has not provided adequate "evidence or reasoning" in support of the enablement rejection. The Action states:

> "In the absence of....data disclosing the effectiveness of an acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 for preventing or treating toxicity in an animal, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims." (June 21, 2006 Office Action, page 6).

It appears from the preceding quotation from the outstanding Action that the USPTO "doubts the truth or accuracy" of the present specification because Applicant has not presented "data disclosing the effectiveness of an acylated derivative of a non-

methylated pyrimidine nucleoside of claim 1 for preventing or treating toxicity in an animal...". This is not sufficient reasoning to shift the burden to the applicant to address this ground of rejection. The USPTO has improperly attempted to shift to the Applicants the burden of presenting evidence that the specification is enabling, contrary to the law under which the PTO bears the burden, in the first instance, of presenting evidence or reasoning in support of its doubts as to the truth of the statements made in the disclosure. Therefore, a *prima facie* case of lack of enablement under Section 112, first paragraph, has not been established in this case. Withdrawal of the rejection on this ground alone is respectfully requested.

Favorable action on this application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:lfm
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100